Vol. 74, No. 5 Established 1884 May 1957

ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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Business Communications address to E. B. TREAT & Co., INC., 45 East 17th Street, New York 3

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LYMPHNODE TUBERCULOSIS A DECISIVE FACTOR IN PULMONARY PATHOLOGY

PH. SCHWARTZ, M.D.*

Warren, Pa.

If we disregard the introduction of new specific healing substances, the development of our knowledge of childhood's tuberculosis in this century is mainly characterized by the following: 1. Definition of the primary complex; 2. recognition of the identity of scrofulosis with lymphnode tuberculosis; 3. the description of regressive ("epituberculous") pulmonary condensations; 4. the observation of the regular occurrence of lymphonodogenous bronchial lesions as the causes of lobular and lobar tuberculous infiltrations.

Today, the occurrence and the nature of primary complexes, the scrofulous syndromes, as well as the reversible pulmonary condensations, seem to arouse but little polemic interest, although many important questions are unresolved in these fields.

The problem of the lymphonodogenous bronchial lesions, however, advanced more and more into the foreground of general interest during the last few years. Numerous bronchoscopic examinations of clinical observers, as well as systematic pathological-anatomical investigations of the present writer, revealed that the discharge of tuberculous lymphnodes into the tracheo-bronchial system regularly accompanies every fresh tuberculous pulmonary

*Professor of Pathology, Anatomy and General Pathology; Former Director of the Pathological Institute of the University of Istanbul (Turkey); Professor of the University in Frankfurt-Main, Germany, on leave of absence; Chief of the Pathological Department of the Warren State Hospital, Warren, Pa.

involvement, and that aspiration-infiltrations developing within the pulmonary tissue, subsequent to the discharge of the necrotic and toxic material of softened lymphnodes, dominate the pathology of pulmonary tuberculosis.

We propose here to comprehensively review these new observations.

1. *Tuberculosis of Intrathoracic Lymphnodes, a Decisive Factor in Pulmonary Phthisis.*

We assume that pulmonary tuberculosis is induced, in the overwhelming majority of cases, by the inhalation of a few, or perhaps even a solitary Koch-bacillus. The first consequence of the infection is the development of an initial ("primary") pulmonary focus, in general, located subpleurally, often subapically and in a dorsal segment, more frequently on the right side. (Figs. 1, 2, 3 and 4).

This initial settlement, generally known as "primary affect", becomes visible to the naked eye 14 days after the infection and presents itself, after an additional 14 to 28 days, as an approximately lentil-sized, irregularly delimitated, massive, caseous focus. (Figs. 2 and 3). At this period, i.e., 4 to 6 weeks after the occurrence of the exogenous infection, the agents reach the regional hilum lymphnodes. Some of these glands already may appear transformed into cherry-sized, necrotic swellings. Then we observe the process to which we devote our entire attention and which seems to explain many, until now, completely enigmatic properties of the pulmonary phthisis.

Three weeks after the entering of the tubercle bacilli into the organism, the lymphnodes involved begin to penetrate the bronchial

---

Fig. 1. . . .Fresh tuberculous primary complex of the right lung. Enlargement and caseous tuberculosis of the parapulmonary (paratracheal and parabronchial) lymphnodes. Fresh lymphonodogenous perforative lesion of the proximal part of the main bronchus of the right upper lobe. Beginning aspiration-infiltration of the right apex. Ubiquitary hematogenous dissemination. 8-year-old boy, who died of tuberculous meningitis. (A. 729/47. Istanbul).

F. . . . . .primary focus near the basis of the right lower lobe.

Probe . . .indicates a small perforative lesion of the proximal part of the main bronchus of the right upper lobe induced by the discharge of a necrotic supraarterial lymphnode belonging to the superior interlobar space of the right lung.

Inf. . . . . .a few, small, fresh apical aspiration-infiltrates of the right upper lobe.

Explanation of all other signs on pages 176-177.

We assume the infection occurred approximately within the final 6-10 weeks, and that the discharge of the necrotic lymphnode began shortly before death.

Fig. 1.

walls. This bronchial *penetration foci*, which appear in the form of mucosal erosions, may induce the development of a bronchogenous spread. Massive, extensive *aspiration-infiltrations*, however, do not appear before 4 to 8 weeks after the beginning of the disease, at a time when large, caseated hilum and paratracheal lymphnodes discharge their necrotic contents, through *perforation ulcers*, into the bronchial system. (Figs. 3, 4, 5).

We observed cavities—*lymphnode cavities*—almost egg-sized, in small children and in adults, indicating the discharge of very large tuberculous lymphnode complexes into the bronchial system; however, the lymphnodes communicating, by solitary or multiple perforative lesions, with the bronchi are most often cherry to plum sized. The perforative mural defects often appear to be very narrow, admitting only a thin probe (Fig. 1.); more frequently, however, they are much wider, permitting the passage of a pencil or even a finger. (Figs. 2, 3 and 5).

The discharging of tuberculous lymphnodes into the bronchial system occurs about 4 to 6 weeks after the onset of the infection. At this time—as experimental investigations revealed—the inflammatory disposition of the infected organism reached its highest degree while, simultaneously, the immunity against Koch-bacilli became highly effective. Thus, in many cases, the lymphonodobronchogenous aspiration infection produces extensive, even giant,

Fig. 2....Fresh primary tuberculous complex of the left lung. Swelling and caseous tuberculosis of paratracheal and parabronchial ("parapulmonary") lymphnodes. Multiple lymphonodogenous perforative bronchial lesions. Beginning development of aspiration-infiltrations of the left lung. Ubiquitous hematogenous dissemination. 15-month-old boy who died of pulmonary and peritoneal tuberculosis. Endocarditis. (A. 249/49, Istanbul).

F.....primary focus near the basis of the left lower lobe.

Probe 1..fresh perforative lesion of the horizontal dorsal bronchus of the left upper lobe caused by the discharge of a caseous supraarterial lymphnode of the medio dorsal interlobar space of the left lung.

Probe 2..fresh perforative lesion of the proximal segment of the lingular bronchus.

Probe 3..large, fresh perforative bronchial lesion of the left main bronchus induced by the discharge of a necrotic tuberculous bifurcation lymphnode.

Inf.....aspiration-infiltration located in the pulmonary sector which is supplied by the lingular bronchus.

inf.....fresh infiltration of the apical sector of the left lower lobe caused by the aspiration of infectious material which was discharged into the left main bronchus by a necrotic bifurcation lymphnode.

All other signs explained on pages 176-177.

We assume that the infection occurred 2-3 months before death and that the necrotic lymphnodes discharged into the bronchial system within the final 2-3 weeks.

Fig. 2.

pulmonary infiltrations which, nevertheless, generally show a distinct tendency to heal, i.e., prove to be benign. (Fig. 4).

The appearance of a lymphonodo-bronchogenous pulmonary aspiration-infiltration often coincides with the first clinical manifestations of a specific pulmonary involvement. The clinical histories of our cases often revealed the onset of cough, fever, and the development of erythema nodosum. This is the time in which the tuberculin reaction becomes positive and in which the tuberculous process may end fatally in meningitis, or—in relatively few instances—in miliary tuberculosis, or sepsis tuberculosa acutissima. Some of the typical complications in this period develop because of the simultaneous discharge of a necrotic lymphnode into the bronchial system and the pleural cavity, and pneumothorax follows. In other instances a softened necrotic lymphnode discharges only into the pleural cavity, or only into the pericardium, inducing pleuritis or pericarditis. Necrotic intrathoracic lymphnodes may also discharge into the esophagus or into intrathoracic vessels. Many lymphonodo-bronchogenous aspiration-infiltrations develop in those subapical (clinically infraclavicular) pulmonary segments which are characteristic of the foci described by Assmann and designated as "early infiltrates" by Simon.

Another typical result of the lymphonodo-bronchogenous dissemination, in childhood tuberculosis, is that type of pulmonary condensation which is known as *epituberculosis*, (Fig. 4.), however, extensive *caseous infiltrations* (Fig. 5.) sometimes filling entire pulmonary lobes are also common. We may add that in many cases which we investigated, those *solitary apical foci* defined by Simon, developed following lymphonodogenous perforative bronchial lesions of the upper lobes. In general, the development of pulmonary condensations in segments of bronchi, affected by lymphnode tuberculosis, is one of the most common occurrences.

Fig. 3....Fresh tuberculous primary complex, fresh perforative bronchial lesion, fresh equisegmental, caseous aspiration-infiltration of the right lung. Fresh, hematogenous dissemination in both lungs. 18-month-old girl, who died of pneumonia. (A. 234/47, Istanbul).
Probe....indicate quite a large lymphonodogenous perforative defect in the anterior wall of the lowest part of the right stem bronchus.
F.....primary focus at the basis of the right lower lobe.
Inf.....aspiration-infiltration located in the apical segment of the right lower lobe.
All other signs are explained on pages 176-177.

We assume that the child was infected 2-3 months before death. The discharge of a necrotic tuberculosis lymphnode complex of the inferior hilum angle occurred approximately 2-3 weeks before death inducing the development of an extensive aspiration-infiltration of the apical sector in the right lower lobe.

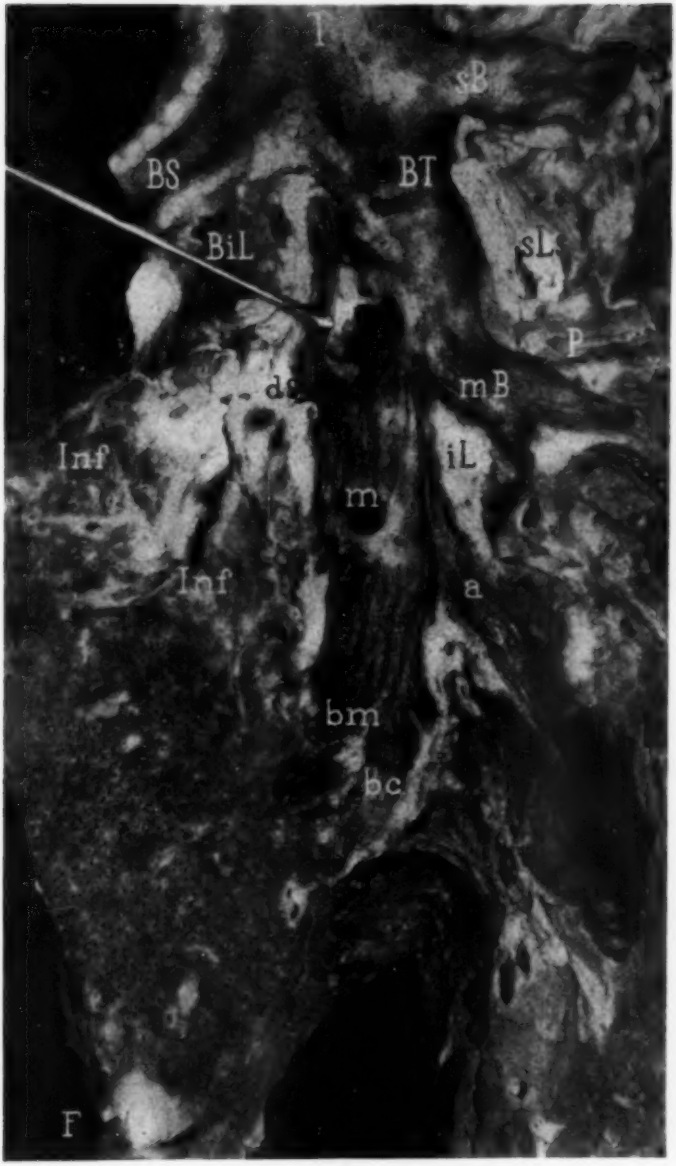

Fig. 3.

Thus, four stages may be distinguished in the initial period of a fresh tuberculous infection: 1. The development of an intrapulmonary initial infiltration (*primary focus, primary affect, start focus*); 2. the specific inflammatory swelling and necrosis of the regional lymphnodes; 3. the discharge of necrotic and softened lymphnodes into the bronchial system; 4. the appearance of equisegmental, (equisectorial) aspiration-infiltrations. All these processes occur during the first three months, subsequent to the entering of the tubercle bacilli into the lungs. Therefore, if we disregard the involvements induced by the obligatory hematogenous dissemination of the agents, which begins as early as two to three weeks after the infection and may end fatally, we understand that *the initial stage of the phthisis is characterized morphologically and defined pathogenetically primarily by the involvement of the parabronchial and the hilum lymphnodes.*

In the great majority of instances *pulmonary tuberculosis constitutes a particularly benign disease,* which practically heals after the initial cycle closes. This benign disposition was proven by many of our observations, in which perforative, bronchial scars of various sizes were observed in combination with equisectorial devastation foci, cicatrical contraction or compensated defects of the pulmonary tissue. (Fig. 6). Bronchial perforative scars often occur even in small children. The younger the individuals who display pulmonary parenchymal cicatrices following perforative bronchial lesions, the more often we will find well developed scars in the segmental bronchi. However, bronchial perforative scars may disappear astonishingly soon after the complete discharge of tuberculous lymphnodes. Nonetheless, a significant combination of parenchymal cicatrices with perforative scars of the segmental bronchi may often be observed many years after the regression of all acute tuberculous manifestations. (Fig. 6).

Indeed, the tuberculous process is not extinguished in every case in which the autopsy reveals bronchial perforative scars, or parenchymal cicatrices. The more thoroughly we proceed, the more often we will find active foci in thoracic or abdominal lymphnodes, even in cases in which no clinical symptoms of a tuberculous disease were present. Encapsulated, even intensely calcified, lymphonodular and pulmonary foci may contain living and highly virulent tubercle bacilli. *Although benign, tuberculosis is a very tenacious disease.* How often we observed fresh tubercular infiltrations of lymphnodes in persons eighty years of age and older, in whom very old bronchial perforative cicatrices witnessed that

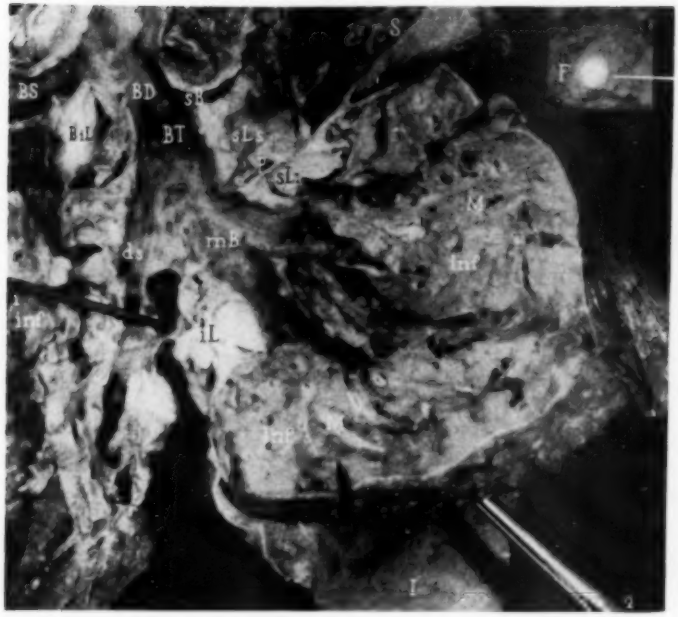

Fig. 4.

Fig. 4....Fresh, tuberculous primary complex of the right lung. Fresh lymphadenogenous perforative lesion of the anterior wall of the right stem bronchus. Numerous lymphonodogenous mucosal erosions of the right stem bronchus. Lobar aspiration-infiltration of the right middle lobe. Primary focus of the right middle lobe. Extensive caseous lymphnode tuberculosis. Ubiquitous, fresh, hematogenous dissemination. 10-month-old boy, who died of tuberculous meningitis. (A. 237/47, Istanbul).

Probe 1..indicates a pea-sized parabronchial lymphnode cavity developed following the discharge of a necrotic tuberculous lymphnode complex of the inferior hilum angle.

Probe 2..indicates the location of the primary focus within the middle lobe. The primary focus was surrounded by the aspiration-infiltration.

F.....primary focus.

Inf.....aspiration-infiltration filling the entire middle lobe.

inf.....aspiration-infiltration located in the apical segment of the right lower lobe.

All other signs are explained on pages 176-177.

We assume that the infection occurred 3-4 months before death, and that the discharge of the tuberculous lymphnode began within the final 2-3 months. The middle lobe displayed a rubber eraser-like consistency, characteristic of reversible ("epitubercular") inflammatory condensations.

a serious attack of the tuberculous process occurred many decades before death!

We assume that a tuberculous infection which starts during childhood and initially produces serious involvements, may regress, persisting, nonetheless, through many decades as a more or less harmless inflammatory process. Latent tubercular foci in lymphnodes, however, may become of decisive importance. Intercurrent diseases, pregnancy, periods of overstrain, of depression, or in general, conditions where nourishment is insufficient, the resistance to tuberculosis may be weakened. Thus, the latent tubercular inflammation, checked by a predominating immunity for many years, is reactivated. Then the involved lymphnodes progressively enlarge and eventually discharge into the bronchi. A new aspiration-infiltration appears, signifying the beginning of a relapse of the pulmonary disease. The accompanying conditions of the new attack—particularly the nutritional state of the patient—decide whether a progressive disease follows, or the healing of the pulmonary involvement. At any rate, later, under favorable circumstances, new lymphonodogenous relapses may occur repeatedly, always ending in encapsulation, calcification, or even complete healing of lymphonodulary and pulmonary foci. It is almost certain that many persons subjected to subsequent minor tuberculous attacks may never become manifestly ill.

Fig. 5....Fresh primary complex of the left lung. Large parabronchial lymphnode cavity due to discharge of necrotic tuberculous lymphnodes. Extensive, caseous aspiration-infiltration of the left upper lobe. Intense enlargement and caseous tuberculosis of the parapulmonary (paratracheal and parabronchial) lymphnodes. Ubiquitous, fresh, hematogenous dissemination, 2-month-old girl, who died of generalized tuberculosis. (A. 598/47, Istanbul).

Probe...penetrates into a cherry-sized, almost empty parabronchial lymphnode cavity communicating with the main bronchus of the left lung.

Ly.....enlarged, necrotic tuberculous lymphnodes of the left intertracheobroncho-pulmonary space located between aorta and trachea. They belong to the group of involved lymphnodes which discharged into the left main bronchus inducing the development of the large aspiration-infiltration of the left upper lobe.

Lc.....parabronchial lymphnode cavity.

Inf.....caseous aspiration-infiltration of the left upper lobe.

Explanation of all other signs on pages 176-177.

This case constitutes one of our most important observations. The mother of this child died, two days after the delivery, of pulmonary tuberculosis. We assume that the infection of the child occurred at birth or immediately after, by the aspiration of infectious material. Thus, this case proves that 2 months are sufficient in the development of a primary tuberculous process to produce extensive lymphonodogenous bronchial perforative lesions and extensive caseous aspiration-infiltrations. We were unable to find a typical primary focus. Therefore, we assume it was enveloped and lost within the large aspiration-infiltration.

The reactivation of an old tuberculous disease may also begin in a pulmonary focus. The conditions for the relapse of the disease in these cases are the same as described above. Soon after the beginning of the exacerbation of the tubercular inflammation,

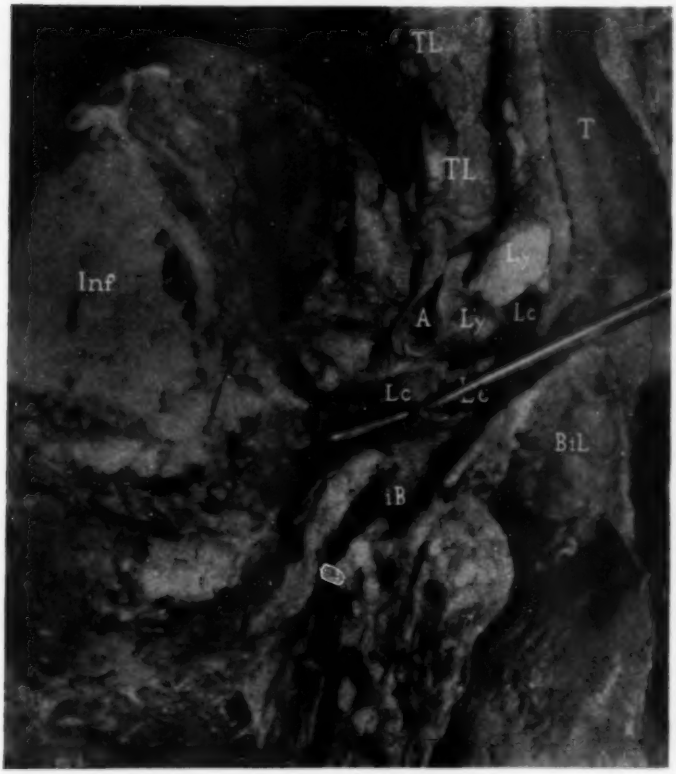

Fig. 5.

vehemently proliferating agents penetrate into the lymphatic vessels and invade the regional lymphnodes, which enlarge, caseate, soften and discharge into the bronchi, inducing the appearance of an aspiration-infiltration. We understand that, even in cases in which the new attack of a chronic tubercular pulmonary process is initiated by an old pulmonary focus, the involvement of lymphnodes is of decisive importance as the new pulmonary infiltration

—and perhaps cavitation—results from a lymphonodo-bronchogenous spread.

Thus, we arrive at a point which has aroused sharp controversy. The traditional theory maintained that a progressive pulmonary tuberculosis in adults begins with the exacerbation of pulmonary foci, developed following a hematogenous spread. According to this teaching, a hematogenous spread of the tubercle bacilli occurs during the primary cycle, originating from the primary focus, or from the secondarily involved lymphnodes, or from both. It is assumed that the bacilli persist for a long period in some foci of hematogenous origin, even in cases in which all other manifesta-

---

Fig. 6. . . Multiple perforative bronchial scars of tuberculous lymphonodogenous origin in the right lung. Multiple, intensely devastated cicatrices of the pulmonary tissue, subsequent to tubercular lymphonodo-bronchogenous aspiration-infiltrations. Absence of bifurcation lymphnodes. Absence of paratracheal lymphnodes below the right subclavin artery. 4½-year-old boy, who died of tuberculous meningitis. (A. 2/52, Wrentham).

Probe 1. . indicates a large perforative scar of the main bronchus of the right upper lobe developed following the discharge of tuberculous lymphnodes of the right intertracheo broncho-pulmonary space, approximately 4 years before death.

Probe 2. . leads to a large perforative scar of the antero-lateral wall of the right stem bronchus, directly above the orifice of the superior dorsal bronchus of the lower lobe. This scar is the sequela of the discharge of tuberculous bifurcation lymphnodes which occurred about 4 yrs. before death.

Probe 3. . shows a perforative bronchial scar directly at the orifice of the axillary bronchus of the right lower lobe. This scar developed after the discharge of tuberculous lymphnodes of the inferior lateral interlobar space of the right lung, which happened approximately 4 yrs. before death. A further, rather large, diverticular lymphonodogenous perforative scar of tuberculous origin was present at the level of the orifice of the median bronchus of the right lower lobe.

Ci. . . . . devastated pulmonary tissue of the right upper lobe representing the cicatrice of a large aspiration-infiltration subsequent to the discharge of tuberculous intertracheo-pulmonary lymphnodes into the main bronchus of the right upper lobe.

ci. . . . . devastated pulmonary tissue of the apical segment in the right lower lobe developed subsequent to an aspiration-infiltration induced by the discharge of tuberculous bifurcation lymphnodes.

cic. . . . . devastated pulmonary tissue of the right lower lobe caused by the cicatrization of an aspiration-infiltration, which developed after the discharge of tuberculous lymphnodes into the axillary bronchus.

Explanation of all other signs on pages 176-177.

In this case large tuberculous lymphnode complexes discharged into the bronchial system approximately 4 years before death. We had the opportunity to investigate the initial pulmonary lesions in radiographies taken at the age of 5 months. At this time, symptoms of a tuberculous meningitis were present. The tuberculous pulmonary and cerebral process regressed under the influence of streptomycin, PAS and promizol. At the age of 4½ years a fatal relapse of the tuberculous meningitis occurred.

tions of the primary cycle healed. Then a relapse of the disease develops from these foci, which enlarge, progressively involving the surrounding pulmonary tissue. Softening of the infiltration

Fig. 6.

and subsequent bronchial, lymphogenous and hematogenous spread are considered responsible for a later aggravation.

The conviction that the hematogenous spread dominates, pathogenetically, the course of a chronic pulmonary tuberculosis, is so deeply rooted that many phthisiologists—as the author often experienced—refused even to consider any other explanation.

To be sure, this is not the sole controversial issue raised by the new observations on lymphnode tuberculosis. In reality, almost all statements by the author, related to these findings were received with sceptical hesitation by certain workers. First, it was asserted that lymphonodogenous perforative bronchial lesions occur in western countries very infrequently; then,—some investigators observed—even if those perforative lesions were present during the development of a tuberculous involvement, they were only of episodic significance, being unrelated to parenchymal pulmonary changes. (Uehlinger, Könn, Dufourt).

On the other hand, the author's endeavor to show the paramount pathogenetic importance of lymphonodogenous lesions was encouraged and endorsed by many phthisiologists, who strove in their lifetime to solve the riddle of pulmonary tuberculosis (Redeker, Simon, Rietschel, Fourestier, Overholt, Wilson).

2. Bronchial Lesions, Frequently were described in Publications, Nevertheless, their Real Significance was Not Recognized. An Attempt to Explain this Strange Fact.

Bronchial and esophageal lesions, caused by tubeculous lymphnodes were first observed by Keir (1784), Sauvée (1802), Hallé (1808), Cayol (1810), Leblond (1824), Becker (1826), Berton (1829), Syme (1835), and Tyce (1843). Berton (1835), Becquerel (1841), as well as Rilliet and Barthez (1840, 1842, 1843) even published comprehensive reviews on this subject more than a hundred years ago. These authors and most of their followers [Vigla (1846), Ward (1850), Edwards (1854), Wunderlich (1856), Bristowe (1857), Fonssagrives (1861), Lebert (1874), Baréty (1874), Weil (1878), Wiederhofer (1878), Barlow (1878), Weigert (1879, 1885), Michael (1885), Kidd (1885), Voelcker (1890, 1895, 1898), Kuss (1898), Pehu (1904)], dealt primarily with *acute cases in children in whom fatal complications appeared.*

Harbitz (1905) and Ghon (1912) found, in systematic investigations, that tuberculous lymphnode perforations often occur in children, while Guéneau de Mussy (1868), Liouville (1869),

Schmidt (1907) and Arnstein (1934) stressed the high frequency of these changes in adults and old people.

In spite of these reports, tuberculous lymphnode perforations into the tracheobronchial system have been, almost generally, considered as practically fatal occurrences which rarely accompany pulmonary tuberculosis in children and almost never in adults. This attitude has not been substantially influenced by tracheobronchoscopic examinations, performed in progressive frequency during the last 50 years. Indeed, the pioneers in this field, [v. Schrötter (1901, 1904, 1907) who was the first to diagnose endoscopically lymphadenogenous tuberculous perforative lesions of both the tracheobronchial system and the esophagus, v. Eicken (1904), Nowotny (1904), Pollak (1906), Erdélyi (1906), Mann (1907), Pauncz and Winternitz (1908), Schmiegelow (1908), Guisez (1909), Hirschland (1909), Jackson (1910)] and their first followers, [Pfeiffer (1919), Hayek (1920), Frank and Gilse (1921), Simon and Jaques (1921), Keiyser and Huizinga (1923), Westergren and Ragnell (1925), Odelberg-Johnson (1926), Hasslinger (1929), Myerson (1930), Eloesser (1932, 1934, 1935), Beutel and Pór (1932), Morlock and Scott-Pinchin; Priesel (1933), Scobie; McConkey; Reinberg; Kanony (1934), Spivek; Faust (1936), Brock, Cann and Dickinson; Vinson and Toone (1937), Sandler; Schneider (1938), Cohen and Wessler (1939), Doyer and Nieuwenhuiyse (1940)] usually proceeded in severe cases. It is noteworthy that Pauncz, who is one of the most illustrious pioneers in this field, considered the discharge of tuberculous lymphnodes into the tracheobronchial system as a sort of spontaneous healing process, as early as 1914. The authors mentioned above dealt in an overwhelming majority of their cases with children.

Many reports of cases of bronchoscopically observed tuberculous lymphonodogenous lesions have been published since 1941. (Dufourt; Mounier-Kuhn; Galy; Boucher; Lowys; Lévi-Valensi; Lemoine; Soulas; Jones, Peck and Willis; Justin-Besançon; Kourilsky; Paley; Lamy; Steiner; Brock; Hutchison; Kraan and Müller; Froste; Carlens and Hellström; Suter and Iselin; Görgényi-Göttche and Kassay; Lewenfisz and Margolisowa; Carez and Bruninx; Laft, Hurst and Robinson; Dahl; Ehrner; Aleman and associates, and many others.) These investigators, examined children primarily, often in instances in which the clinical healing of the perforative bronchial lesions could be observed. Some of the authors reported up to 60 per cent positive bronchoscopical findings in cases of active pulmonary tuberculosis.

In a monograph published in 1952, we collected hundreds of papers published during the last 150 years, reporting on thousands of cases in which tuberculous lymphnodes discharged into the tracheobronchial system, the esophagus and intrathoracic vessels. *A connection between lymphonodogenous tracheobronchial lesions and tuberculous pulmonary processes was mentioned, however, in only a few of these communications, without any emphasis. Undoubtedly the real significance of the phenomenon only became obvious a few years ago.** Considering these astonishing facts, we must find an appropriate explanation.

We feel that *the causes for this failure are rooted in the history of medicine.* We consider one of the causes to be the *vague demarcation between the so-called scrofulosis and tuberculosis, as well as pulmonary phthisis.* Certain theories, suggested by Laënnec, aimed at connecting pulmonary tuberculosis, (the condition known today as miliary tuberculosis), and pulmonary phthisis (i.e., pulmonary disease characterized by caseo-pneumonic infiltrations and showing a tendency to cavitation). However, the doctrine, resolutely sustained by Virchow, that "scrofulosis" (a disease primarily characterized by lymphnode swelling) "tuberculosis" and "phthisis" constituted three different conditions, prevailed almost until the last decade of the past century. As tracheobronchial perforative defects were mainly observed in children, and the accompanying excessive enlargement of lymphnodes were considered manifestations of "scrofulosis", no one associated pulmonary infiltrative processes, occurring simultaneously, to lymphonodogenous bronchial lesions. Scrofulosis generally was considered a benign condition, which often disappeared spontaneously, while phthisis and tuberculosis (miliary tuberculosis) were regarded as fatal diseases. We assume, the opinion shared even today, that voluminous tumescences of lymphnodes, and consequently, lymphonodogenous bronchial lesions do not occur in adults, constitute a late heritage of the old scrofulosis doctrine. If the opinion that scrofulosis was not a tubercular condition was not so deeply rooted, Eliasberg-Neuland's theory of "epituberculosis" could not have developed either.

Another historic fact weighing heavily is that *neither scrofulosis nor pulmonary phthisis were considered to be infectious diseases.* This concept was vindicated by no less an authority than R. Vir-

*Before 1947, the present author collected about 100 cases in which the autopsy disclosed lymphonodogenous perforative bronchial lesions of tuberculous origin; he registered all, preserved and photographed many of them without understanding the phthisiogenic significance of his observations!

chow, not only after Villemin's publications (1867), but even after the discoveries of R. Koch. In view of this situation, how could one conceive the idea that a necrotic lymphnode—be of scrofulous or of tuberculous nature—discharging into the tracheobronchial system, could induce a pneumonic infiltration, characteristic of pulmonary phthisis? This probably is the source of the opinion which induced certain clinicians and pathologists, even in the last few years, to regard the appearance of tubercular lymphnodogenous bronchial lesions as episodes without real significance. (Terplan, 1955).

Scrofulosis, tuberculosis and pulmonary consumption were considered, for centuries, to be *hereditary constitutional diseases.* It was assumed that these conditions were present at birth and ready to develop under favorable circumstances. This opinion prevailed even toward the end of the past century.

The transmission of the predisposition to descendants was naturally considered a function of the parents' "blood". It was assumed that this hereditary predisposition manifest itself wherever scrofulous, tubercular, or caseo-pneumonic and cavitary foci appeared. Furthermore, it was presumed that a kind of endogenous infection developes, inducing the appearance of a noxious substance within scrofulous and caseo-purulent foci, a "materia" which being disseminated by the blood stream would produce tuberculosis (i.e. miliary tuberculosis).

After Koch's discovery in 1882, the meaning of "tuberculosis" profoundly changed, becoming more and more general, while the concept of "scrofulosis" faded and "phthisis" simply became the name of a particular manifestation of tuberculosis. Now, according to the new micro-biological facts, P. von Baumgarten (1882) modified the old theory of a hereditary predisposition. He taught that the descendants "inherit" *tubercle bacilli* which, being located by preference in thoracic lymphnodes, or within the pulmonary apices, may persist in a latent and inactive state for years and even decades, until they have an opportunity to provoke a malady.* Soon the old and newer theories were modified by the discovery of the tuberculous pulmonary primary complex, initiated by Parrot (1876) and developed by Hervouet (1887), Kuss (1898), E. Albrecht, H. Albrecht (1909), and Ghon (1912). Accordingly, the hematogenous dissemination, which presumably produced the latent phthisiogenic foci, was thought to originate from the

*Baumgarten defended this theory as late as 1925.

primary period. It was asserted that the hematogenous spread might occur at the period in which the primary complex flourishes, or perhaps later, during an intercurrent episode, passing clinically unsuspected, or immediately before the manifestation of a fresh pulmonary disease.

We note, the first assumption was that an hereditary *predisposition* was transmitted by the "blood" of the parents to their descendents; later it was asserted that the blood of the unbilical cord transmits *bacilli*. Eventually, the idea of an intra-uterine transportation of microbes was definitely discarded. Nevertheless, the hypothesis persisted that latent tubercular foci of hematogenous origin exist and that the initial foci of a chronic pulmonary tuberculosis in adults were remnants of hematogenous disseminations.

These theories undoubtedly lost much of their power of conviction. However, they are, even today often invoked to explain apical tuberculosis, early infiltrates, as well as lesions appearing simultaneously or successively in different pulmonary segments, in cases in which the process of the chronic pulmonary phthisis establishes itself and then develops without obstacle.

EXPLANATION OF THE SIGNS IN THE FIGURES.

We employ for the abbreviation of the names of the pulmonary lobes, the tracheobronchial system, the paratracheal and parabronchial lymph nodes, the vessels, and the parapulmonary spaces the following:

A aorta; *P* pulmonary artery; *sc* subclavian artery; *S* upper lobe; *M* middle lobe; *Li* lingula; *I* lower lobe; *BD* right main bronchus; *BS* left main bronchus; *BT* stem bronchus; *b* bronchus in general.

Bronchi of the upper lobes.

sB main bronchus of the upper lobe; *ha* ant. horizontal axillary bronchus; *hp* post. horiz. axillary bronchus; *hd* horizontal dorso-paravertebral bronchus; *oa* ant. oblique bronchus; *op* post. oblique bronchus; *va* ant. vertical bronchus; *vp* post. vertical bronchus.

Bronchi of the (right) middle lobe.

mB main bronchus of the middle lobe; *ma* anterior branch; *mp* post. branch.

Bronchi of the lingula.

lB main bronchus of the lingula; *ma* ant. branch; *mp* post. branch.

Bronchi of the lower lobes.

iB main bronchus of the lower lobe; *ds* superior dorsal bronchus of the lower lobe; *dd* descending branch of the sup. dorsal bronchus; *m* median bronchus; *a* axillary bronchus; *ac* paracardial branch of the axillary bronchus; *di* inferior dorsal bronchus; *bl* lateral basal bronchus; *bc* central basal bronchus; *bm* medial basal bronchus.

The parapulmonary spaces.

TBP intertracheo-broncho-pulmonary space; *B* bifurcation space; *Is* superior lateral interlobar space of the right lung; *Ii* inferior lateral interlobar space of the right lung; *Il* lateral interlobar space of the left lung; *Imd* medio-dorsal interlobar space.

Lymph nodes.

LL lymph nodes in general; *TL* paratracheal lymph nodes; *Ly* paratracheal lymph nodes, located below the right subclavian artery; *sL* lymph nodes of the superior

lateral interlobar space of the right lung; *sLs* supraarterial lymph nodes of the sup. lat. interlobar space of the right lung; *sLi* infraarterial lymph nodes of the sup. lat. interlobar space of the right lung; *iL* lymph nodes of the inferior lateral interlobar space of the right lung; *lL* lymph nodes of the lateral interlobar space of the left lung; *mL* lymph nodes of the medio-dorsal interlobar space; *mLs* supraarterial lymph nodes of the medio-dorsal interlobar spaces; *mLi* infraarterial lymph nodes of the medio-dorsal interlobar spaces; *BL* bifurcation lymph nodes; *BLd* right bifurcation lymph nodes; *BLs* left bifurcation lymph nodes.

Branches of the pulmonary artery.

The same symbols as for the concurrent bronchi, only in the place of *B* or *b*, *A* or *a*: (for example; main artery of the middle lobe: *mA;* or, axillary artery of the lower lobe: *aa*).

(To be concluded in the June Issue)

GROWTH OF JUVENILE DIABETICS. (Acta endocrinol., 15:133-165, Feb. 1954). Bergquist presents observations on 56 diabetic children of Malmö, Sweden, in whom diabetes became manifest before the age of 15. In 21 of these children, diabetes appeared before the age of 5, in 17 between the ages of 5 and 10, and in the rest between 10 and 15 years. The children were treated with insulin, and most of them received a liberal diet without sweets. During an observation period averaging 5.3 years, a general but not severe retardation of growth was observed, it was most pronounced in boys. This indicates that delayed growth is part of the morbid picture in juvenile diabetes. Even under the strictest management, it is likely that the body's lack of insulin is seldom fully compensated. The greater tendency to growth disturbance in diabetic boys than in diabetic girls is possibly explained by a defective gonadal function, as androgens are obviously of importance for the growth of boys whereas estrogens do not have the same influence in girls. There were only three diabetic dwarfs among the diabetic children observed in Malmö, but the author found eight other diabetic dwarfs in two other districts in Sweden. Observations on these 11 diabetics with definitely retarded growth indicated that a constitutional factor contributed to the retarded growth in height. The majority had received a diet low in calories and carbohydrates and, probably because of this, received small insulin doses. At least 9 of the 11 patients had hepatomegaly Delayed development of the genitals or indications of hypogonadism or both were encountered in all cases. The hypogonadism was probably of hypophysial origin. The low 17 ketosteroid values found in the girls likewise indicate a deficiency of adrenocortical steroids, which is possibly of a hypophysial origin. Animal experiments have demonstrated that insulin is essential for normal growth, and clinical observation on diabetic children suggests that their retardation in growth is largely the result of lack of insulin.—*J.A.M.A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Lawrence B. Slobody, at New York Medical College, New York, and Doctor Walsh McDermott, at Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

HYPERVITAMINOSIS A

ROGER C. BRESLAU

New York.

(Continued from April issue)

ACUTE VITAMIN A TOXICITY

Until 1951, reports of acute poisoning due to the ingestion of large single doses of vitamin A were exceedingly rare but they did appear occasionally when, for example, a child swallowed an entire 50 cc. bottle of fish-liver concentrate (containing approximately three million I.U. of vitamin A). It was noted by Bills[5m] that the only clinical manifestations in such cases were transient nausea and vomiting. However, in May 1951, Marie and See[4s] reported three cases of acute vitamin A poisoning in infants aged seven and a half months, three and a half months, and three months. In addition to symptoms of frequent vomiting and drowsiness, there occurred a marked bulging of the anterior fontanel. This alarming sign was observed by the parents, and constituted the basis for seeking medical attention. Neither cervical rigidity, neurological signs, nor systemic symptoms developed during the illness. Lumbar puncture showed clear fluid under increased pressure, but perfectly normal in every other respect, both chemically and cytologically.

After careful questioning of the parents, it was established that within twenty-four hours prior to the development of symptoms, each child had received the contents of an ampoule containing 350,000 units of vitamin A and 300,000 units of vitamin D. In the next few months, three additional cases came to the attention of Marie and See, all showing nearly identical manifestations. In all cases, recovery was complete within one or two days, either spontaneously or following lumbar puncture.

In order to eliminate any role that the supplementary vitamin D might have played in the disorder, Marie and See studied the re-

sults of administering vitamin A alone to infants in oral doses of 350,000 I.U., and in three cases out of six succeeded in producing acute benign hydrocephalus. They were unable, however, to produce abnormal symptoms with synthetic vitamin A, or by subcutaneous injections of the natural vitamin (60,000 to 90,000 units). At any rate, these results established the fact that vitamin A alone, given in massive oral dosage, was responsible for these transitory incidents.

The consistent clinical picture in these cases, plus those in a large number of other infants[47-53] who presented acute disorders after ingestion of a single massive dose of vitamin A have led Marie and See[54] to describe a special syndrome (which now bears their names), characterized by the following signs:

1. *Functional Disorders.* Within twelve to twenty-four hours after ingestion there is almost always repeated projectile vomiting, perhaps diarrhea, and usually discomfort, agitation, and either insomnia or drowsiness. Four of the infants showed a rise in temperature to 39°C. Most of them did not gain weight for forty-eight hours, and one infant in their series lost weight.

These disorders were, however, not proportional to the severity of the hydrocephalus, in fact, they were perhaps more nearly inversely proportional. The child whose fontanel had bulged most intensely demonstrated no functional disorders whatever, and the spinal fluid was normal except for elevated tension. This child had received a total of 300,000 units of vitamin A over a period of six days in the form of nose drops containing 50,000 I.U. per gram.

2. *Clinical and Laboratory Features.* The essential characteristic feature is the isolated nature of the distended fontanel, which in the most typical cases produces an actual mushroomlike protuberance on the child's head. There are no signs of meningeal irritation, and no neurological abnormalities. The blood pressure, fundus oculi, ear drums, and EEG are all consistently normal. The spinal fluid is consistently normal, both chemically and cytologically, but is regularly under slightly elevated tension, which, however, is not proportionate to the height or tension of the fontanel. Vitamin A is never found in the spinal fluid.

The blood levels of vitamin A are of course strikingly increased, but the most bulging fontanels were not accompanied by the highest blood levels of vitamin A. In absorption tests in fasting infants, Marie and See found that blood values reached from 400 to

714 I.U./100 ml. from an average starting value of 102 I.U./100 ml. The magnitude of the rise in each child was proportionate to his fasting level at the start, and generally reached five times that value.

Acute hydrocephalus, therefore, certainly is produced by oral ingestion and absorption of a massive amount of natural vitamin A, and is probably due to an excessive secretion of cerebrospinal fluid as evidenced by an increase in cerebrospinal fluid pressure. The hydrocephalus develops in parallel with the increase of blood vitamin A levels, but with a lag of a few hours.

Marie and See[55] also succeeded in reproducing the syndrome of acute hydrocephalus in puppies from three to four months old, by means of oral administration of vitamin A. Single doses of 350,000 I.U. by mouth produced a very distinct tension of the fontanel. After six hours, the blood vitamin A level reached 1700 I.U./100 ml. The other puppies took only the oily solvent (with vitamin A destroyed), and showed no abnormal signs. Two other puppies received 100,000 units daily for three successive days and also showed no abnormalities. In the dog then, as in the human, vitamin A produces an acute and transitory hydrocephalus, providing one gets a massive and rapid absorption as reflected by a steep rise in the plasma vitamin A level.

Marie and See, after careful follow-ups, feel that the acute hydrocephalus, with its intensive bulging of the fontanel, is a transitory and harmless disorder, both in its immediate and remote prognoses. Nevertheless, they feel that it is extremely undesirable to have such a potent drug available in such enormous dosages, and have campaigned to have the potency of the preparations reduced. In 1954, at their request, the preparation was restandardized in a lower, though still excessive dosage of 70,000 I.U. in the hope of avoiding further accidents through self-dosage.

The minimal amount of vitamin necessary to produce acute symptoms in the adult is not precisely known, but may be estimated to be in excess of one million units. There have been occasional reports of vitamin A poisoning in adults following the ingestion of a single massive dose. Getz and his associates[10a] administered 50 cc. of halibut liver oil (three million units of vitamin A) in a single dose to four adults. One individual was considered normal, and the remaining three were diagnosed as having borderline vitamin A deficiencies when their plasmas were analyzed by biophotometric methods. All experienced dull headaches after the huge dose, but had no other symptoms. Rodahl

and Moore[21] cite the case of a man engaged in the manufacture of halibut liver oil at the Crookes Laboratories, who helped himself to four or five ounces of the oil daily, without instruction. After five days he became severely ill, the main symptom being marked giddiness. The daily dose had been about 7,500,000 units. After the use of the oil had been discontinued, he rapidly recovered, and felt and appeared normal within eight to ten days.

One of the earliest descriptions of poisoning due to eating liver of the polar bear was given in the logbook of Gerritt de Veer, written during the hibernation of the Dutch polar explorer Willem Barendsz on Nova Zembla in 1596[12]. Another early description of acute polar bear liver toxicity was mentioned by the arctic explorer, Elisha Kane, in 1857 (cited by Knudson and Rothman)[10a]. The symptoms among his party were "severe diarrhea, vertigo, and their concommitants." Jackson,[10a] in 1899, recounted the illness that befell members of his exploration party upon eating polar bear liver. Six men suffered severe frontal and occipital headaches six hours after ingestion of the liver, with a feeling of nausea, and one man had spells of vomiting and a more prolonged illness.

Lindhard (cited by Rodahl[21a]) has reported another expedition in 1913 in which nineteen men became ill after eating a stew containing bear liver. The symptoms included drowsiness, sluggishness, irritability, an irresistable desire to sleep, severe headache and vomiting. On the second day, the skin of ten of these men began to peel around the corners of the mouth, beginning in spots and gradually spreading over larger areas. In some cases the peeling was confined to the face, but in several cases it was generalized.

Other explorers have since reported one or more of the symptoms mentioned in the above accounts, the most recent incident being in 1940. Headache is the most important manifestation, and was described by two men in Stefansson's[10a] expedition as violent, localized in the forehead and eyes, and as being the worst either of them had ever suffered. Nausea, vomiting, vertigo or giddiness, drowsiness, and irritability are other commonly reported findings, and all of these appear to be referable to increased intracranial pressure, most likely due to elevated cerebrospinal fluid pressure as in the infantile cases described by Marie and See.[46,54]

Several cases of chronic hypervitaminosis A have been reported which provide a connecting link between the manifestations of acute and chronic vitamin A overdosage. In the report by Gribetz

and his associates (case 2),[23] a 17 month old girl exhibited an enlarged head, prominent forehead, and asymmetrically placed anterior fontanel. Pneumoencephalogram and ventriculograms revealed slight dilatation of the ventricles. A history of seven months of excessive vitamin A intake (240,000 units/day) was elicited from the mother. Following withdrawal of vitamin A, the head assumed normal proportions. Naz and Edward's[35] patient showed enlargement of the head, and a noticeable venous pattern in the bridge of the nose which extended onto the forehead. The blood vitamin A level was 1121 I.U./100 ml.

In the light of what has been shown by Marie and See[34] concerning the ability of massive doses of vitamin A to produce cerebrospinal fluid hypertension, it is reasonable to assume that both of the children mentioned above had increased intracranial pressure with resulting hydrocephalus, probably as a result of overstimulation of the choroid plexus by excess vitamin A. However, in addition, these patients showed the classical signs of chronic vitamin A overdosage: anorexia, irritability, pruritus, loss of weight, refusal to walk, elevated alkaline phosphatase levels, elevated plasma vitamin A levels, and subperiosteal cortical hyperostoses favoring the ulnae, clavicles, tibiae, fibulae, and metatarsals.

Gerber, Raab and Sobel[31] reported the case of an adult female who manifested very pronounced signs of acute vitamin A toxicity only at the outset of her disorder, but went on to develop a full-blown syndrome of chronic hypervitaminosis A in addition to her cerebral symptoms. Her initial symptoms were diplopia, severe frontal headaches, and nausea. In addition, she had begun to suffer incontinence of urine. She had pronounced nystagmus on lateral gaze, and the fundi showed bilateral papilledema and engorgement of the veins. Mentation and consciousness were in no wise impaired, and there were no neurological abnormalities. Direct ventriculograms showed some dilatation of the lateral ventricles.

During the course of her intoxication, which lasted eight and a half years, she was hospitalized ten times. Before the correct diagnosis of hypervitaminosis A was arrived at, the following diagnoses had been considered: brain tumor, serous meningitis (for which she underwent a right subtemporal decompression), chronic encephalitis, viral radiculoencephalitis, and psychoneuroses. By the time she came to the attention of the above authors, she had gone on to develop extremely severe chronic manifestations of der-

matologic and skeletal injury which completely overshadowed her persisting cerebral symptoms.

These chronic manifestations included loss of hair, excruciating pruritus, complete "poker-like" rigidity of the spine, unremitting intense generalized skeletal pains, and inability to walk. Nevertheless, she still continued to show the cardinal sign of acute vitamin A toxicity, in that the site of the subtemporal decompression, which had been done nearly eight years previously to relieve the suspected serous meningitis, was still tense and bulging although the fundi were now normal, and diplopia and nystagmus were absent. During this long interval of suffering, the patient had "faithfully" continued to consume 500,000 units of vitamin A daily, in the form of a self-prescribed preparation, which by the way, was free of vitamin D.

Ten weeks after this prodigious intake of vitamin A had been stopped, the decompression site became completely soft, and remained so thereafter. If this patient is acknowledged to have had serous meningitis, vitamin A toxicity must be added to the list of known causes of this condition.[31] It cannot be known whether dural venous sinus thrombosis was also present in this case, but there is enough evidence extant to show that excessive production of cerebrospinal fluid almost certainly results from acute vitamin A toxicity. No other explanation can satisfactorily account for the persistence of a tense, bulging decompression site during seven and a half years of excessive vitamin A intake, and its sudden spontaneous reduction with cessation of vitamin A intake.

Persistent severe headache with visual disturbances, vertigo, nausea, and vomiting, in the absence of focalizing neurological signs comprises, then, a most characteristic symptom complex arising from acute vitamin A toxicity in both infants and adults, and appears to be the result of increased intracranial pressure due to an oversecretion of cerebrospinal fluid. For this presumption, we have the following impressive body of evidence:

1. Numerous case reports (over 50) of infants with bulging fontanelles and associated cerebral manifestations of acute transient hydrocephalus.[46-54]
2. Violent headaches and cerebral symptoms in cases of polar bear liver poisoning.[10a,21]
3. Persistent meningeal hypertension and visual disturbances in Gerber's patient.[31]
4. Enlargement of the head in the chronically intoxicated patients described by Gribetz,[23] and by Naz and Edwards.[35]

The phenomenon of internal hydrocephalus may also then explain the exophthalmos which was consistently produced in rats be Lewis and Cohlan with massive doses of vitamin A in aqueous suspension. Striking exophthalmos has also been observed by a number of other investigators,[14,16,19] in laboratory animals receiving high dosages of vitamin A, and has been personally observed by Josephs[1] in a child. Sulzberger and Lazar[28] reported slight bilateral exophthalmos in their adult patient. Bifulco's case[30] presented marked bilateral pulsating exophthalmos, which was accompanied by very severe headaches. The fundi disclosed abnormal pulsations of the retinal veins. Cerebral angiography failed to disclose the suspected aneurism, and this fact, coupled with the recession of the exophthalmos and the disappearance of pulsations in one eye after the withdrawal of vitamin A probably indicates some causal relationship to excess vitamin A intake. However, headaches were still present in this patient, six months after cessation of vitamin A overdosage.

It is quite obvious that the symptomatology and physical findings following a single massive dose of vitamin A are strikingly different from the manifestations of chronic intoxication with vitamin A, although, as described above, they may occasionally overlap. The two pure forms, however, are so widely different as to be comparable with the difference between acute and chronic states of heavy metal poisoning, with the exception, of course, that in vitamin A overdosage, either acute or chronic, the prognosis is uniformly excellent. It is also obvious that the long incubation period and insidious onset characteristic of the chronic disorder are completely absent in the acute form of toxicity. The effects in acute intoxication are almost certainly independent of supersaturation of liver storage depots, and seem to be a manifestation of direct toxicity for specific tissues, as well as being further evidence of the ability of vitamin A to induce accelerated cellular activity.

HYPERVITAMINOSIS A IN PREGNANCY

Until fairly recently, there has been no information available concerning possible injury to the fetus as a result of the administration of excessive doses of vitamin A during the early months of pregnancy. As was aptly expressed by Knudson and Rothman,[10a] "realization that the critical period for injury may be only a matter of a few hours suggests the need for experimental work on this subject." However, in 1953, Cohlan[5a] reported on his success in producing congenital anomalies in baby rats by feeding

excessive amounts of vitamin A to the mothers during pregnancy. In his first study[59], 150 female rats were mated, and 100 of them were then given massive doses of an aqueous dispersion of vitamin A for varying periods during their pregnancies. These animals received 35,000 I.U. of vitamin A daily by mouth for periods varying from thirteen days to twenty-one days following conception, while 50 control animals were kept on an ordinary diet of proprietary pellets, receiving no extra vitamins. Some of them, however, received the dispersing agent without the vitamin A. All of the animals were sacrificed at or near term, and the young were examined for gross deformities.

In the control group, 44 out of 50 rats produced litters with a total of 410 normal young being formed. Thus, 88 percent of the animals of the control group had successful pregnancies. But, of the 100 mated rats which had received massive doses of vitamin A, only 10 percent carried young successfully to the end of the study. Fifty-eight percent of the animals whose mothers had received large prenatal doses of vitamin A showed congenital defects, whereas *no* congenital defects had been observed in the control group. Cranial deformities were most consistently present in the young of the test group. This deformity consisted of an extrusion of the brain to the external surfaces of the head with only a membranous film overlying the exposed brain surface. In addition to skull deformities, other congenital defects were noted sporadically, such as harelip, cleft palate, and defects in eye development.

In a more recent study, Cohlan,[60] using larger groups of animals, achieved close agreement with his previously reported findings, and in addition, found that in the rat the period from the seventh day to the tenth day of gestation was the time of the most critical susceptibility to the teratogenic effects of excess vitamin A. Only 25 litters with 148 offspring (of which 77, or better than half, were malformed) were obtained from 210 mated females which had received 35,000 I.U. of vitamin A daily from the second, third, or fourth days of gestation to the sixteenth day. The abnormalities observed included protrusion of part or all of the forebrain, malformation of the eyes, cleft palate, shortening of the mandible and maxilla, and spina bifida with meningocele and hydrocephalus. From 100 untreated control animals, 84 litters were obtained, with 831 offspring, all normal. It is significant that daily doses of 15,000 I.U. of vitamin A did *not* result in fetal malformations.

Gebauer[61] has similarly reported success in producing congenital anomalies in rats following administration of massive doses of

vitamin A to their mothers during pregnancy. Giroud and Martinet[62,63] have made the interesting observation that hypervitaminosis A during pregnancy can also cause total resorption of the embryo. Albino rats were given 20,000 to 35,000 I.U. of vitamin A daily from the fourth to the sixteenth day of gestation, and were sacrificed on the twenty-first day. In twenty-four pregnancies, 65 percent of the embryos were totally absorbed. In those pregnancies in which some embryos were retained, 61 percent were alive, while the remainder were dead and in process of resorption. In the survivors, there was a high incidence of malformations, with cleft palate occurring in 51 percent of the animals. Exencephaly and ocular abnormalities occurred also, but with less frequency.

The results of these experimental studies would certainly suggest the rashness and great potential danger of overzealous and unjustified self-dosage with large amounts of vitamin A during pregnancy. Similarly, the practitioner should give careful consideration to the possible consequences before instituting massive therapy with vitamin A during pregnancy, unless he is prepared to perform regular determinations of the vitamin A blood level.

DISCUSSION

Accurate diagnosis and successful treatment, both curative and prophylactic, of disorders caused by vitamin deficiency stand high among the major triumphs of medicine in this century. However, ever since vitamins have been used as therapeutic agents, there have been sporadic reports of ill effects following their administration. In the early days following their discovery, the vitamins were dispensed only in the relatively dilute forms in which they occur in natural foodstuffs, so that low potency preparations such as cod liver oil could be safely sold without prescription for uncontrolled use at home. Thus the belief arose, and still persists uncorrected today, that all vitamin preparations are totally benign and innocuous. The prevalence of this belief is responsible for such statements from patients as, "how could anything so beneficial as a vitamin be harmful?", or, "I thought that if a little dose was good for Johnny, a big dose would be better."

The belief in the complete harmlessness of vitamins is no longer tenable, however, and has not been so for quite a number of years. There is now a massive body of evidence that prolonged feeding of excessive amounts of highly potent concentrates of fat-soluble vitamins A and D are seriously, and in the case of vitamin D, sometimes fatally toxic. As a result of the widespread availability

of these potentially toxic high potency preparations to the general public without restriction, a new man-made disorder has made its appearance during the last few decades—*hypervitaminosis.*

The control of vitamin D poisoning in the general population is still not a major public health problem for several reasons. First of all, the extreme seriousness of vitamin D poisoning is widely recognized by members of the medical and allied professions, and large quantities of vitamin D are not readily sold across the counter without some careful questioning by the pharmacist. Secondly, vitamin D-containing products are standardized to relatively low potencies compared with the concentration of other available vitamins, and massive excesses are not present in preparations other than those designed for selected therapeutic uses. For the most part then, excessive dosage with vitamin D is still in the hands of physicians, and almost without exception, hypervitaminosis D has developed only in patients who have intentionally received massive doses of vitamin D as therapeutic adjuncts in the treatment of rheumatoid arthritis or tuberculosis. These are calculated risks taken by physicians, and not by patients on their own initiative.

In contrast, most recorded cases of vitamin A poisoning have resulted from prolonged daily feeding of excessive amounts of vitamin concentrates to infants by their mothers, who either increased the prescribed dose to toxic levels on their own initiative in ignorance of the potential dangers, or who misunderstood the directions given by their doctors, although in each case the correct dosage was clearly stated on the manufacturer's label on the bottle. However, in no case does a manufacturer's label warn of the toxic effects of prolonged overdosage, nor have mothers in general been so advised by pediatricians. The failure to point out clearly the dangers of feeding excessive amounts of vitamin concentrates represents a serious error of omission, and deserves to be corrected in the future.

In many cases of hypervitaminosis A, the diagnosis can be made only in retrospect. This is due perhaps to two major barriers: (a) a low index of suspicion, and (b) the great difficulty in obtaining an admission from a mother that she has been administering huge doses of vitamin A to her baby. Only after the child has totally recovered, and the mother is satisfied that she has not been guilty of causing permanent injury, may she sheepishly admit her overzealous indiscretion.

Customarily, in pediatric history-taking, the doctor's interest in

vitamins is directed exclusively at insufficiency of intake, and the question of excessive intake is not even raised. If overdosage is to be detected early from the history, the actual amounts and frequency of feeding, the method of measuring the amount, and the type of preparation used must all be sought for in detail. A statement of the frequency and amount of vitamin concentrate purchased may be more informative than the mother's impression of the unmeasured daily dose. Apparently, it is not uncommon practice for mothers to stop measuring vitamin concentrate accurately, drop by drop, soon after they start its use; to save time, the estimated dosage is poured directly from the bottle into a teaspoon. Under these circumstances, the error of estimate appears to be invariably in the direction of overdosage. The possibility of confusion between Oleum Percomorphum (60,000 I.U./gm.) and cod liver oil (850 I.U./gm.) at the time of purchase should also be borne in mind. Apparently, the impression that the former is just a brand-name variation of the latter is not too rare.

The poisoning of otherwise healthy children by the superfluous feeding of vitamin A concentrates is especially regrettable because it is probable, according to J. M. Lewis,[8] that there is no deficiency of vitamin A in ordinary infantile and juvenile diets in the U.S.A. The huge liver stores of vitamin A in the healthy members of the populaton of this country are maintained not only by the general excellence of the American diet, but also by vitamin enrichment of foods, and by the administration of vitamins to poultry and dairy animals, and to nursing mothers. Lewis has maintained throughout the years that "there is no good reason why a healthy infant or child taking a normal formula or diet should receive added supplements of vitamin A," and further concludes that "the hazards of vitamin A poisoning from routine prophylactic feeding of vitamin concentrates A and D appear to be greater than the hazards of vitamin A deficiency in healthy infants and children *not* fed vitamin A concentrates." Bransbey and his associates [2d] further support the contention that supplementation of the diet with vitamin A concentrates is superfluous for normal children. They concluded, after a study of 1620 English schoolchildren, that vitamin A supplementation has no effect on growth, strength, nutrition, incidence or severity of clinical disease, or absenteeism from school.

The prodigious potency of some available preparations certainly stands high among the list of factors contributing to more and more cases of hypervitaminosis A. The ready availability, for

example, of an extremely high potency preparation, such as "Vitadone Forte" (containing in a single ampoule, 350,000 units of vitamin A) was no doubt responsible for the veritable "rash" of acute toxic accidents that occurred in Europe between 1951 and 1954 (at least fifty cases). However, in 1954, at the request of Marie and See (who originally described the syndrome[46]), the drug was restandardized in a lower (though still superfluous) dosage of 70,000 units, in the hope of avoiding further accidents.

It is about time that a similar restandardization was undertaken in this country. Lewis[6] feels and many agree, that the possibility of vitamin A poisoning would be much more remote if the concentration of vitamin A in all non-prescription preparations were standardized to 5,000 or 10,000 units per cc. (instead of the present 50,000 to 65,000 I.U. per cc.[USP•BP]). Furthermore, Lewis feels that even the size of the containers should be restricted to a capacity of 10 cc. or 15 cc., rather than 50 cc., since even overzealous mothers would be less likely to give one or two teaspoonfuls of an expensive preparation when the bottle only contains half an ounce. It is to be hoped that manufacturers will eventually be required to meet regulations of this type. It is not too unreasonable to demand also that any vitamin A preparation not conforming to this safety standard be required to carry the label: *Caution—May be Harmful If Used in Excess of Recommended Dosage.*

Thus far, we have concentrated upon the dangers of overdosage in pediatric practice, but at this point it would be well to also stress that the administration of massive doses of vitamin A for long periods in the treatment of skin, eye, ear and gynecological disorders would certainly seem to be an intemperate and even hazardous procedure. Nevertheless, large doses of from 100,000 to 500,000 I.U. daily, and even more, have been advocated in the treatment of many conditions (such as acne vulgaris) for which there is little rational justification.[28,31a,33,57,58] Fortunately, in most adult patients, the zone between adequate prophylactic and therapeutic dosages, and toxic levels, appears to be very wide.[38] Nevertheless, Sulzberger and Lazar wisely caution that the physician administering large doses of vitamin A must be on the lookout for signs and symptoms of toxicity, and should have regular analyses for plasma vitamin A levels performed on all patients on high dosage schedules for periods of more than a few weeks. This precaution is especially necessary in the case of pregnant women, if we may draw any conclusions from the valuable work of Cohlan, and others regarding the ability of massive doses of vitamin A during pregnancy to produce congenital abnormalities in rats.

In view of the widespread (and not infrequently indiscriminate) consumption of vitamin A by the general population, it is extremely surprising that only four cases in adults have been reported thus far. This would tend to indicate either that vitamin A in excess is much more benign for adults than it is for children, or that the signs of poisoning in adults are less frequently recognized by physicians. There is certainly evidence for both points. However, in view of the ritualistic vitamin dependency of many adults, it is probable that minimal signs of toxicity develop in many persons, but before a diagnosis can be established, cessation of excess vitamin A intake comes about spontaneously or coincidentally with the prescription of other medication. Thus, the true etiology of the symptoms may never come to light, and the condition continues to remain unrecognized by the practitioner. Nevertheless, Gerber's case[31] serves to remind us that chronic vitamin A poisoning in an adult can be a very serious and crippling disorder, and that its early diagnosis can forestall a great deal of expense and suffering.

The commonest cause of diagnostic error in this disorder is still a faulty history of the precise amount of vitamin intake. It has already been stressed that routinely taking a vitamin history may prove inestimably valuable in pediatric practice. However, internists as well as pediatricians are frequently confronted by patients who have unexplained headaches, constipation, pruritus, dryness of the skin, and anorexia. It is worth the trouble in such cases to carefully question the individual about any unusual degree of vitamin consumption. Certainly, if there are vague bone and joint pains in conjunction with a history of a vitamin habit or "fad," a plasma vitamin A determination should be carried out. The association of vague generalized complaints with an elevated serum vitamin A level may point to mild forms of the disorder, and help the physician to abort the progression of vitamin A intoxication before clinical manifestations become intense and disabling.

The folly of highly suggestible persons with regard to their faith in the "magical properties" of vitamins is exemplified by Sulzberger's patient,[28] an overenthusiastic woman, who on hearing from a "nutrition commentator" on a radio broadcast that vitamin A is good "for alleviating dry throats and as a prophylaxis against colds," began a daily intake of 600,000 units of a vitamin A concentrate, which she continued for eighteen months, with occasional supplemental sprees of one to two million units when impending dry throats or colds were suspected. However, it has been well established by reliable observers that the use of vitamin

A preparations in great excess of normal requirements to reduce the incidence of colds or other respiratory infections is of absolutely no proven value in individuals whose intake of vitamin A is already adequate.[3e,3f,9,10,12] The experiments which support this point are numerous, and many of them have been briefly reviewed by Clausen,[9] who concludes that no justification exists for terming vitamin A an "anti-infective vitamin."

Interruption of growth and increased vulnerability to bacterial invasion are secondary manifestations of a specific disturbance in the metabolism of epithelial membranes resulting from vitamin A deficiency. One of the results of this disturbance is keratinization and loss of cilia in the respiratory epithelium, and dystrophy of the lacrimal glands. Both of these structures tend normally to sweep out bacteria-laden foreign particles, and thus combat infections. And indeed, there is no doubt that individuals suffering from severe vitamin A deficiency are prone to develop infections of the eyes and respiratory tract, and that the administration of vitamin A in such cases is beneficial, but only through restoration of the protective epithelium to normal, rather than by any specific action upon the invading organisms, or the host's immune responses. Nevertheless, vitamin A has been popularly but erroneously termed the "anti-infective vitamin," and it is this term which is responsible for the widespread misconceptions which exist regarding its value in preventing and combatting infections.

The therapeutic value of vitamin A rests solely upon its action in those conditions resulting from its deficiency. Its use is also indicated where there is good reason to suspect inadequate intake or impaired absorption of the vitamin, or where accelerated tissue repair is in process, as in post-operative states. As an aid to the development of bodily resistence to infection, it would be of value only when the stores of the vitamin in the body are exhausted, or the intake inadequate. At present, there is no evidence that vitamin A preparations have any therapeutic action other than that of relieving vitamin A deficiency.

Culver[8] has put his finger exactly on the pulse of the problem by calling our attention to the astounding magnitude of vitamin consumption in this country. The sale of vitamins during 1947 amounted to $188,000,000 of which $26,000,000 worth was sold without prescription by mail-order houses, department stores, grocery stores, and variety stores. The annual sale of costly high potency preparations increased threefold between 1945 and 1947, from $15,000,000 to $45,000,000. The public has long been over-

stimulated on the subject of the need for supplementary vitamins, and it will be exceedingly difficult for the individual physician to protect even his own patients against the flood of commercial exploitation of vitamins which gushes endlessly from newspapers, magazines, radio broadcasts, and television programs. In truth, he himself is kept busy enough warding off the "assaults" which are directed at him from representatives of the pharmaceutical houses and from advertisements in the medical journals.

The medical facts, though, are conclusive—vitamin A concentrates are probably superfluous, certainly expensive, and potentially dangerous in the hands of overzealous mothers for routine daily administration to healthy infants and children. They are equally dangerous when they are consumed indiscriminately and intemperately by adults, or when they are prescribed for therapy in conditions which do not call for the specific actions of vitamin A. However, medical control of vitamin A in the home is very difficult because the public gets most of its information concerning the "magic" of vitamins from commercial advertising, which is understandably designed to create public belief that there is a widespread need for daily supplementary intake of vitamin A, that daily supplements prevent and cure a host of indefinite common complaints, and that vitamin A concentrate is a harmless and benign substance in any dosage. By all means, until the whole truth becomes common knowledge to members of the laity and medical profession alike, all authentic cases of vitamin A poisoning should continue to be carefully recorded and widely published in the medical literature.

CONCLUSIONS

1. Prolonged consumption of excessive amounts of vitamin A leads to serious and distressing manifestations of chronic toxicity. The pathological changes in bone and in epidermal structures are attributable to a markedly high elevation of vitamin A blood levels over a continuous period of several months.

2. There is much evidence to suggest that the disorder is far more widespread in the general population than the present paucity of reports in the literature would suggest. The steep increase in the number of cases reported each year indicates that many cases of hypervitaminosis A probably have been overlooked in the past.

3. The diagnosis of hypervitaminosis A should not be difficult for the practitioner with a high index of suspicion. Three factors must be present in order to confirm such a diagnosis:

(a) a history of recent excessive intake of vitamin A; (b) recognition of a characteristic set of clinical and roentgenographic features; and (c) the demonstration of an elevated serum vitamin A level.

Once the diagnosis has been made, prompt and complete reversal of the syndrome may be accomplished by the elimination of all vitamin A from the patient's diet.

4. The importance of routinely obtaining a history of recent vitamin intake, particularly in pediatric practice, cannot be stressed too highly. Faulty history taking constitutes by far the major source of diagnostic error in this disorder.

5. In the absence of demonstrated impairment of intestinal function, or other conditions which render intake or absorption inadequate, most authorities contend that the amounts of vitamin A and its precursors contained in the ordinary diet of the American child are more than sufficient to supply his minimum daily requirements of these factors, and that vitamin A supplementation for otherwise healthy infants and children is wholly superfluous.

6. It is well established that the use of vitamin A preparations in great excess of normal requirements to reduce the incidence of colds or other respiratory infections is of absolutely no proven value. The therapeutic value of vitamin A rests solely upon its action in those disorders arising from its deficiency. Its use, therefore, in massive doses to treat a wide variety of non-specific disorders by laymen and practitioners, is greatly to be deplored.

7. The failure of manufacturers to point out clearly the dangers of excessive dosages of high potency concentrates represents a serious error of omission. It is, therefore, suggested that in the future such preparations be labeled with a suitable warning of the potential dangers of excessive doses. Furthermore, it is suggested that preparations which are intended for routine prophylactic use in the home should be restandardized to low potency levels, if they are to remain free of prescription restrictions.

SUMMARY

1. A comprehensive discussion of several major aspects of the subject of vitamin A intoxication is presented, in which detailed consideration is given to the symptomatic manifestations and differential diagnostic features of the syndrome in both its acute and chronic phases.

2. A fairly complete historical review of the investigations in

this field, both clinical and experimental, is outlined. For many years it has been known that excessive intake of vitamin A would produce spontaneous bony fractures, multiple massive haemorrhages, and death in small animals, but it was not until 1944 that the symptom complex was recognized for the first time in man. Even now, awareness of its fairly common occurrence is only slowly becoming widespread among practitioners, the disorder having been regarded as little more than a medical curiosity for quite a number of years following its initial description.

3. The occurrence of acute toxic incidents following the ingestion of single massive doses of vitamin A is described. The clinical and laboratory features of this acute syndrome are discussed in considerable detail, with particular reference to the symptoms arising from accelerated production of cerebrospinal fluid. The striking differences between the symptomatology and physical findings of the acute toxic state and those of chronic hypervitaminosis A are emphasized.

4. The recent finding that excessive doses of vitamin A during pregnancy results in a high percentage of congenital deformities in the rat is presented. In this regard, the possible potential dangers of massive administration of vitamin A to humans during pregnancy are considered.

5. A plea is made for wider recognition of the condition of mild or borderline hypervitaminosis A by the practitioner, particularly through more careful attention to details of the recent vitamin intake history. It is also felt that more effective restrictions should be imposed upon the availability to the general public of potentially harmful preparations containing inordinately large amounts of vitamin A.

6. An extensive bibliography is appended containing many pertinent references to reports of both acute and chronic hypervitaminosis A in humans, as well as to the majority of recent publications in the experimental field.

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TYPHOID IN PREGNANCY AS CAUSE OF NEUROPSYCHIATRIC DISORDERS IN INFANTS: THREE CASES. M. SCHACHTER. (Rev. españ. pediat., 12:665-670, Sept.-Oct. 1956).

Typhoid in the course of pregnancy may be the cause of neuropsychiatric disorders in the infants. Three cases are reported in children of 5, 5, and 3 years of age. In the first case, the mother had typhoid during the first month of pregnancy. The child was born at full term. When the child was observed at the age of 5 years, she showed deformities of the ears, anisodactylism and isodactylism, and signs of an operation for correction of palatine fissure and harelip. She was mentally retarded and had severe behavior disorders. The other two mothers had typhoid fever when they were in the fifth month of pregnancy. Both children had convulsions. One of them had symptoms suggestive of whooping cough for 9 months. Both children had severe behavior disorders.

J.A.M.A.

DEPARTMENT OF ABSTRACTS

Conducted by
MICHAEL A. BRESCIA, M.D., NEW YORK

LEWIS, D. and TIDWELL, R. A.: CHLORTETRACYCLINE FOR PROPHYLAXIS OF STREPTOCOCCAL DISEASE. (Northwest Medicine, 55:1218, Nov. 1956).

Forty-three children received 125 mg. of chlortetracycline daily for a 2-year period in order to prevent recurring streptococcal infection. No beta hemolytic S. break-throughs occurred in 834 nasopharyngeal cultures. The normal coliform bacteria of the intestinal tract were either depressed or eliminated, but returned under continued therapy. Furred tongue occurred in one patient, but later the tongue became normal. There was no depression of blood components during the two years of prophylaxis. Chlortetracycline can be used as a prophylactic agent against beta hemolytic S. AUTHORS' SUMMARY.

GLASER, J.: THE PROPHYLAXIS OF ALLERGIC DISEASE WITH SPECIAL REFERENCE TO THE NEWBORN INFANT. (New York State Journal of Medicine, 55:2599, Sept. 15, 1956).

The subject of the prophylaxis of allergic disease in infancy and childhood is discussed. It is suggested that certain factors in the management of the diet of the pregnant mother of a potentially allergic infant may be helpful; the best feeding for the prophylaxis of allergic disease in the newborn, potentially allergic infant is human breast milk with the nursing mother on the same diet as advocated during pregnancy. If the mother cannot or will not nurse her infant, the substitution of soybean milk for cow's milk (or some other substitute for cow's milk) from birth, or from the time of the abandonment of breast feeding is urged. It is shown that such a procedure will reduce the incidence of major allergic disease before the age of six years from about 60 per cent to 15 per cent.

The problem as to whether or not there has been a progressive increase over the years in the relative frequency of allergic disease in children is discussed. Reasons are given indicating that if this actually is the case, the explanation could very well be the gradual abandonment of breast feeding which has taken place in this country over the past 25 or 30 years. AUTHOR'S SUMMARY.

GREGER, W. P. and STEELE, M. R.: HUMAN FETOMATERNAL PASSAGE OF ERYTHROCYTES. (New England Journal of Medicine, 256:158, Jan. 24, 1957).

The average unagglutinated-red-cell count of fourteen mothers of Group A who bore infants of Group O was probably significantly higher at delivery and showed a significantly greater decline six weeks post partum than that of nine mothers of Group A who bore infants of Group A. This finding is thought to imply the presence of fetal erythrocytes in the maternal circulation in normal pregnancies and indirectly to emphasize the role of vigorous maternal antibody-forming ability in the pathogenesis of erythroblastosis fetalis. AUTHORS' SUMMARY.

DURAND, P. AND SALOMONE, P.: TWO INFANTS WITH BLOCKED HYDROCEPHALUS WERE CURED FOLLOWING PNEUMOENCEPHALOGRAPHY. (Aggiornamento Pediatrico, 7:525, Sept. 1956).

The authors report on two cases of hydrocephalus in infants of one month and eight days and another of four months. Both of these were congenital and pictures and x-rays of the skull demonstrate the typical findings of hydrocephalus. However, following the diagnostic pneumoencephalography, both infants showed a recession in the size of the head and follow-up some two years later showed infants with normal sized heads and with apparently normal mental development. M.A.B.

Douglas, J. W. B.: Mental Ability and School Achievement of Premature Children at 8 Years of Age. (British Medical Journal, 4977:1210, May 26, 1956).

This is the fourth of a series of papers describing the growth and development of a national sample of premature children — that is, weighing 5½ pounds (2.5 kg.) or less at birth — who, with a carefully matched group of controls, have been followed through from birth. Tests in reading vocabulary, and intelligence were given to these premature children and to their controls when they were 8 years of age. Premature children scored less than their controls in each of these tests, being proportionately the most handicapped in reading. The handicaps of premature children did not increase significantly with either falling birth weight or decreasing length of gestation. In general, the handicaps found were small, but there was a well-defined group with no obstetric or genetic explanation for their low birth weight, who were heavily handicapped in all tests. AUTHOR'S SUMMARY.

BOOK REVIEWS

Conducted by
MICHAEL A. BRESCIA, M.D., NEW YORK

THE AMERICAN FLUORIDATION EXPERIMENT. By F. B. Exner, M.D. and G. L. Waldbott, M.D. Edited by James Rorty. Cloth. Pp. 241. Price $3.75. Devin-Adair, 1957.

A definitive up to date report has been written by two eminent physicians on the subject of fluoridation of water supply. The evidence and strength of the arguments against fluoridation are a revelation and in strange contrast to the overwhelming barrage of favorable sentiment appearing in the regular channels of communication. This paradox is by no means accidental as the authors point out. The Public Health Service has resorted to propaganda in favor of fluoridation and has succumbed to many of the evils which are attendant upon a dogmatic position. When officialdom arrogantly assumes an air of infallibility and an attitude of indifference to the public, then serious danger lurks in high places. While many opponents of fluoridation rest their case on moral and constitutional grounds, there exists an abundance of scientific evidence which demonstrates the alarming danger of fluoridation.

Writing with cold objectivity and with precision, the authors dissect and expose the barrenness of the claims favoring fluoridation unmercifully, but with a scholarly distinction. How a program of such magnitude, resting as it does on such a feeble foundation, has achieved such popularity is a deplorable tribute to the machinery of propaganda and a disheartening commentary on the superficiality of some so-called experts. The engineering difficulties and dangers in fluoridating water are presented in a chapter which should make the readers thankful for the water engineers who apparently know their business well.

This should be required reading for medical and dental societies at all levels and all public health commissioners. Chairmen of public health committees are duty bound to read this book and report to their parent organizations which all too often have endorsed fluoridation in parrot-like fashion totally unaware of the case against fluoridation. Proponents of fluoridation must refute the charges contained therein, an unenviable task. Opponents of fluoridation will find an armamentarium of considerable dimensions. The writers and publisher have rendered a needed service with this book.

S. J. BAUDO, M.D.

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